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(54) Title: TARGETED DELIVERY OF DRUGS TO THE LOWER GASTROINTESTINAL TRACT

(57) Abstract

This invention relates to compositions for the treatment of certain diseases of the distal intestinal tract. Specifically, the invention relates to coated delivery vehicles such as nonporous microspheres, microscapsules, non-crosslinked porous beads or liposomes, for the sustained delivery of a therapeutically effective amount of an active agent. The composition is coated with a substance, e.g., a polysaccharide such as pectin, which is specifically attacked by intestinal bacteria to permit the release of the active agent in the distal intestinal tract, particularly the colon.

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TARGETED DELIVERY OF DRUGS TO THE LOWER GASTROINTESTINAL TRACT

BACKGROUND OF THE INVENTION

A. Field of the Invention

This invention relates to the treatment of diseases of the distal intestine, especially the colon, such as inflammatory bowel disease. More particularly, it relates to delivery vehicles and methods for the targeted delivery of an active agent to the distal intestinal tract.

B. Description of the Prior Art

Many intestinal diseases (e.g., inflammatory bowel diseases such as ulcerative colitis and Crohn's disease) either originate or are expressed in the lumen or the tissue lining the lumen of the gastrointestinal ("G.I.") tract.

Current therapies for treating G.I. diseases usually involve systemic drug administration, even though the intended target of beneficial drug action may be a particular region of the G.I. tract. Generally, a relatively high systemic concentration is necessary in order to ensure an effective local concentration of the drug. An example of this is the administration of a steroid to treat inflammatory bowel disease. The steroid is given to elicit a local action but is administered systemically. Continued or prolonged systemic exposure to a steroid may result in atrophy of adrenal glands or cause other undesirable side effects. Steroids have also been administered by enema, but this does not prevent systemic absorption.

Prodrugs have been used to minimize systemic side effects. A prodrug is a substance which is itself substantially inactive at therapeutic concentrations, but undergoes a transformation after ingestion to yield an active species. The active species then performs its activity, primarily in the tissue where transformation occurred. Thus, the effects of the active species will be essentially limited to the region where the transformation takes place. An example of a prodrug therapy is the use of sulfasalazine for inflammatory bowel disease.

While the prodrug approach has worked for some drugs, it is limited in scope due to its dependence upon the specific chemistry of the drug, prodrug, and G.I. environment. A new prodrug must be developed, if possible, for different active species and conditions to be treated.

International Application WO 91/16881 (hereby incorporated by reference) describes colonic delivery systems comprising a drug in combination with a matrix. The matrix comprises a saccharide-containing polymer resistant to chemical and enzymatic degradation in the stomach and small intestine, which polymer is degraded in the colon. The matrix is prepared separately, and then combined with a drug.

SUMMARY OF THE INVENTION

The present invention is directed to controlled release delivery vehicles for the targeted delivery of therapeutic active agents to the distal intestinal tract. These controlled release delivery vehicles are useful for the treatment of gastrointestinal pathologies of the distal intestine, such as ulcerative colitis, Crohn's disease, colon cancer and infectious diseases of the colon.

The controlled release delivery vehicles used herein comprise nonporous microspheres, microcapsules (prepared from linear or crosslinked materials), non-crosslinked porous beads or liposomes, which enclose one or more active agents.

The controlled release delivery vehicles of the present invention may also be a dosage form such as tablets or capsules comprising the active agent-containing nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes as described above.

The active agents (for example, a corticosteroid) will generally be present in the amount of 1-100 mg., frequently in the amount of about 5-20 mg.

The active agent-containing delivery vehicles are coated with a polysaccharide such as pectin, and ingested orally. The active agent is not released until enzymes normally present in the distal intestine remove the polysaccharide so that the delivery vehicle containing the entrapped active agent is released. The active agent is then gradually released to the affected region in a controlled fashion from the delivery vehicle.

The polysaccharide-coated delivery vehicles may also be layered with an enteric blocking agent, which further protects the coated delivery vehicles from contact with and degradation by stomach acids and proximal intestinal enzymes and digestive agents.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises methods and delivery vehicles for the targeted delivery of therapeutic agents to the distal G.I. tract.

The delivery vehicles include nonporous microspheres, microcapsules, non-crosslinked porous beads and liposomes, which enclose one or more active agents, or a dosage form such as capsules or tablets comprising the active agent-containing nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes as described above.

The delivery vehicle is coated with a substance resistant to intestinal degradation, such as a polysaccharide, which allows the delivery vehicle to pass through the proximal G.I. tract and release the active agent at the affected region. For example, for the treatment of ulcerative colitis in which only the large intestine (a portion or its entire length) is affected, the delivery vehicle is coated in order to initially remain intact in the G.I. tract and to degrade in or near the large intestine. For the treatment of Crohn's disease in which both the terminal ileum and the ascending colon are affected, the delivery vehicle is coated in order to initially remain intact in the G.I. tract until reaching the junction of the ileum with the colon and then degrades so as to release the active agent in that region.

In one preferred embodiment, the polysaccharide is pectin. The active agent is not released until enzymes normally present in the colon react with pectin and remove it from the delivery vehicle so that entrapped active agent is then gradually released in a controlled fashion.

I. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

The term "delivery vehicle" denotes a composition which comprises one or more active agents and is designed to release the active agent(s) in a controlled fashion. The term "delivery vehicle", for the purpose of this invention, encompasses nonporous microspheres, microcapsules, non-crosslinked porous beads, liposomes, or a dosage form such as tablets and capsules comprising the nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes as described.

The term "active agent" denotes a substance or composition which is suitable for therapeutic or diagnostic purposes and may be incorporated into the delivery vehicle. An active agent may be a vaccine, a hormone (*e.g.* insulin, erythropoietin or hydrocortisol), a drug or a vitamin (*e.g.*, vitamin B-12). Examples of active agents include anti-infectives (antibiotics such as antibacterials, fungicides or antiparasitic compounds), anti-inflammatory agents, antihistaminics, anticholinergics, mydriatics, antivirals, antimitotics, carbonic anhydrase inhibitors, anesthetic agents, peptides, proteins, diagnostic agents and/or immunosuppressive agents. Preferred examples of active agents useful in the present invention are corticosteroids such as hydrocortisone, beclomethasone dipropionate, tixocortol pivalate, dexamethasone, prednisone, budesonide, prednisolone, and triamcinolone acetonide. Also preferred are nonsteroidal anti-inflammatory agents for treatment of inflammatory bowel disease, antitumor agents for treatment of colonic malignancies, antiparasitic agents for treatment of parasites, and antibiotics for treatment of infections.

The term "dosage form" refers to a composition which comprises an active ingredient and pharmaceutically acceptable excipients. Examples of dosage forms include, for example, tablets and capsules.

The phrase "effective amount" refers to a dosage sufficient to produce a desired result. Generally the desired result is an objective or subjective improvement of an intestinal disease or condition. The active agent, such as a corticosteroid, will generally be present in a composition in the amount of 1-100 mg., frequently in the amount of about 5-20 mg.

The terms "controlled", "sustained" or "time release" delivery denote that the active agent is released from the delivery vehicle at an ascertainable and manipulatable rate over a period of time, ranging from about thirty minutes to about 3 days. The release rate may vary as a function of a multiplicity of factors. An important determinant of the rate of delivery is particle size, particle composition, particle hydration, acidity of the medium (either internal or external to the matrix), and solubility of the active agent in the intestinal environment.

The term "targeted delivery" refers to the delivery vehicle which is formulated to deliver the active agent at a specific site where the treatment of a disease or medical condition is needed.

The term "microparticles" refers to a delivery vehicle comprising a plurality of small particulates approximately 1 to 500 μm in diameter, composed of an active agent and a matrix compound, for example a polymer, that limits and controls the release of the active agent. For the purpose of this invention, the term "microparticle" encompasses nonporous microspheres, microcapsules, non-crosslinked porous beads, liposomes and the like.

The term "nonporous microspheres" refers to a delivery vehicle which has the active agent and matrix components dispersed throughout the variably shaped, roughly spherical particles. That is, the internal structure is a

matrix of the agent and an excipient, usually a polymeric excipient. In general controlled-release microspheres release the active agent at a declining rate (first-order). But microspheres can be designed to release agents at a near zero-order rate.

The term "microcapsules" refer to compositions wherein a matrix or encapsulating material is used to enclose gases, liquids, or solids into particles of relatively small size (0.02-500 μm). A microcapsule has its encapsulated material (i.e., an active agent) centrally located within a unique membrane, usually a polymeric membrane. This membrane may be termed a wall-forming material, and is usually a polymeric material. Because of their internal structure, permeable microcapsules designed for controlled-release applications release the active agent at a constant rate (zero-order rate of release). Hereinafter, the term "microcapsules" will include nanocapsules, microbubbles (hollow particles) and porous microbubbles and particles in general that comprise a central core surrounded by a unique outer membrane.

The term "non-crosslinked porous beads" refers to porous compositions comprised of linear or branched homopolymers or copolymers. A preferred embodiment comprises macroporous particles prepared from rigid polymers such as polystyrene or poly(methyl methacrylate).

The term "liposome" refers to any bilayer structure that encloses a volume, such as a micelle. The most common example is a phospholipid liposome. Membrane lipids which are suitable for the formation of a bilayer are diverse and include the following classes of compounds: phospholipids, lysophospholipids, glycosyl diacylglycerols, plasmalogens, sphingomyelins, gangliosides, and sterols. The term liposome encompasses both multilamellar (multiple bilayers that form concentric shells much like an onion) and unilamellar

structures. These typically have diameters between 200 and 5000 Angstrom.

The term "distal intestinal tract" is used interchangeably with "large intestine" and denotes the cecum, appendix, colon and rectum, especially the colon. "Near" the large intestine denotes the distal segment of the small intestine, particularly of the ileum.

The term "enteric blocking agent" is a compound, molecule or composition that, when surrounding a central moiety, solid core or cavity, protects the moiety core or cavity and their contents from contact with and degradation by stomach acids and proximal intestinal enzymes and digestive agents. An example is Eudragit™.

II. Preparation of Delivery Vehicles

As those skilled in the art will appreciate, the nature and size of delivery vehicles strongly influence the release rate of the active agent contained therein, and of the rate of absorption and efficacy of biological effect produced by the active agent. Smaller particles will release an active agent at a more rapid rate than larger particles due to their relatively larger surface area.

II.A. Nonporous Microspheres

Nonporous microspheres can be formulated utilizing a variety of methods currently known in the art. One method comprises dissolving an active agent and a matrix component in a compatible solvent, and then removing the solvent, for example through rotary evaporation or vacuum evaporation. Removal of the solvent yields a composition wherein the active agent is dissolved or dispersed within the matrix component.

Particles can be created utilizing grinding or milling techniques as known in the art. Another method comprises dissolving the matrix component in an appropriate solvent and adding the active agent which is then coacervated to precipitate the matrix component and therefore encapsulate the active agent.

II.B. Microcapsules

Microcapsules may be prepared by many methods, including coacervation, interfacial polymerization, mechanical methods, polymer dispersion and matrix encapsulation. There is voluminous literature on the preparation and use of encapsulating polymers designed for sustained drug release (for example, U.S. Patent No. 5,238,714, issued Aug. 24, 1993 to Wallace, et. al.; Bechtel, W. Radiology 161, 601-604 (1986); and EPO 0302582, Feb. 8, 1989 by Tice et al.). The matrix material is selected according to the intended use of the microcapsules.

II.C. Non-crosslinked Porous Beads

The non-crosslinked porous beads are formed by suspension polymerization in a liquid-liquid system. In general, a solution containing monomers, a polymerization catalyst (if used), and an inert but fully miscible liquid is formed which is immiscible with water. The solution is then suspended in an aqueous solution, which generally contains additives such as surfactants and dispersants to promote the suspension. Once the suspension is established with discrete droplets of the desired size, polymerization is effected (typically by activating the reactants by either increased temperature or irradiation). Once polymerization is complete, the resulting rigid beads are recovered from the suspension. The beads at this point are solid porous structures, the polymer having formed around the inert, water-immiscible liquid, thereby forming the pore network.

II.D. Liposomes

There are many types of liposomes that can be used in various routes of drug administration [see Gregoriadis (ed.) in Liposome Technology, 2nd edition, vol I-III, CRC Press, Boca Raton, Fla., 1993]. Certain types of liposomes can provide a controlled, sustained release system (Mezei M: In Controlled Release Dosage Forms & Tipnis HP (ed.): Bombay College of Pharmacy, India, 1988, pp 37-46). In such a system, the rate of drug release is primarily determined by the liposome's physicochemical properties. Liposomes can be tailored for a specific application by modification of size, composition, and surface charge to provide the desired rate of drug delivery (Meisner D, et al: In Proceedings, 15th International Symposium on Controlled Release of Bioactive Materials. 15:262-263, 1988; Mezei M: In Drug Permeation Enhancement, Theory and Application; Hsieh DS (ed.): Marcel Dekker Inc., New York, 1993, pp 171-198; and Meisner D, et al: J Microencapsulation 6:379-387, 1989). Liposomes as a delivery vehicle for insulin and heparin have also been described (see, for instance, U.S. Pat. No. 4,239,754; Patel et al. (1976) FEBS Letters Vol. 62, page 60; and Hashimoto et al. (1979) Endocrinol. Japan, Vol. 26, page 337).

Materials and procedures for forming liposomes are well-known to those skilled in the art and need not be described herein in detail. For example, U.S. Pat. Nos. 4,485,054, 4,761,288 and 4,937,078, the disclosures of which are hereby incorporated by reference, disclose suitable liposome preparation techniques. As described therein, the liposomes can be prepared as multilamellar lipid vesicles (MLV), unilamellar lipid vesicles, including small unilamellar vesicles (SUV) and large unilamellar vesicles (LUV) and as multivesicular liposomes. Many other liposome manufacturing techniques also can be used to make the final liposomal product containing the appropriate active agent, lipids, and other excipients, as will be understood by those skilled in

the art. For example, suitable liposomes also can be prepared using the known ethanol or ether injection methods. Lipid components are usually phospholipids and cholesterol; excipients are tocopherol, antioxidants, viscosity inducing agents, and/or preservatives.

Phospholipids are particularly useful, such as those selected from the group consisting of phosphatidylcholines, lysophosphatidylcholines, phosphatidylserines, phosphatidylethanolamines, and phosphatidylinositols. As noted, such phospholipids often are modified using, for example, a modifying agent selected from the group consisting of cholesterols, stearylamines, stearic acid, and tocopherols. The lipid typically is dissolved in a solvent and the solvent then is evaporated, typically under a reduced pressure, to yield a thin lipid film containing any lipophilic agent. Afterwards, the film is hydrated, with agitation, using an aqueous phase containing any desired electrolytes and any hydrophilic agent, and lipid vesicles entrapping the agent are produced. As recognized by those skilled in the art, while certain materials and procedures may give better results with certain active agents, the use of particular materials and procedures are not narrowly critical and optimum conditions can be determined using routine testing. Additionally, as also noted, a preservative or antioxidant often will be added to the preparation.

The formation of a stable liposome requires the temperature to exceed the gel-to-liquid crystal-transition temperature (Tc). This corresponds to the melting point of the acyl chains. All phospholipids have a Tc and this depends on the nature of the hydrophilic head and the degree of unsaturation on the hydrocarbon chain. The membrane formation is strongly influenced by the preparation conditions, primarily heat, light and pH.

The interior of the lipid bilayers can be probed with a variety of a standard techniques including Raman and FTIR spectroscopy as well as proton NMR. Differential Scanning Calorimetry (DSC) is often used to obtain information on the thermodynamics of membrane formation.

The multilamellar vesicles or lipid membranes are often very heterodisperse with respect to size. The particle diameter is often lowered by exposing the vesicles to ultrasonication. The size is generally measured through liquid chromatographic techniques.

The liposomes my be coated with a variety of substances that enhance their specificity. For example, they may be coated with antibodies, in addition to the pectin (U.S. Patent No. 5,258,499 issued Nov. 2, 1993 to Konigsberg).

II.E. Capsules or Tablets

Capsules and tablets are prepared by methods well known in the art. For example, tablets are prepared by compression of a mixture comprising the active agent-containing nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes which enclose one or more active agents and pharmaceutically acceptable excipients. The capsule formulation is prepared by filling the gelatin capsules with the active agent-containing nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes in admixture with pharmaceutically acceptable excipients.

Suitable pharmaceutically acceptable excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like.

III. Coating Materials

The microparticles containing the active agent(s) are treated to control the release of the active agent in the affected region of the G.I. tract. In the present invention, two different kinds of coating materials are used.

III.A Polysaccharide Coating

The key to obtaining release of the active agent from the delivery vehicle in or near the colon lies in the use of a coating that is not breached or significantly removed until it reaches the colon. In general, the coating may be on the microparticles containing the active agent or on the exterior of a dosage form such as tablets or capsules comprising the active agent-containing microparticles, or on both. Where the dosage form is a tablet, "coating" of the microparticles may be obtained by compressing a mixture of particles with the coating material. The term "coating" is thus used herein in a broad sense where the microparticles or dosage form are substantially surrounded by the "coating" material.

The substances used for the coating are polysaccharides. Examples of polysaccharides include pectin, arabinogalactose, chitosan, chondroitin sulfate, cyclodextrin, dextran, galactomannan (guar gum) and xylan. A preferred polysaccharide is pectin.

The amount of polysaccharide coating on the microparticles or the dosage form will depend on the particular polysaccharide selected, but in any event will be of sufficient thickness to remain intact until reaching the colon. Thus, in the case of the preferred polysaccharide pectin, it has been shown that dissolution and release will depend on the particular pectin selected and primarily its methoxy content. Thus, pectins with a high degree of

methoxylation demonstrate a higher degree of protection for the microparticles or the dosage form than those pectins with a lower degree of methoxylation.

Pectin USP with a degree of methoxylation of 70% is an example of a preferred material which can be obtained from Bulmer Pectin, UK. The thickness of coating will depend on where it is placed in the dosage form. If the microparticles themselves are coated, the thickness will be at the thinner end of the range, while a coating on the entire dosage form may be at the higher end of the range. A useful coating thickness range is from about 0.1 mm to about 1.0 mm.

III.B. Enteric Coating

The outer coating is an enteric coating designed to protect the delivery system from the acid environment of the stomach. Such coatings are well known and are designed to dissolve once the neutral, or slightly alkaline environment of the intestinal tract distal to the stomach is reached. Thus, such coatings do not control delivery of the active agent to the distal intestinal tract. Enteric coatings suitable for use in the present invention are disclosed in U.S. Patent No. 5,316,774 for "Blocked Polymeric Particles Having Internal Pore Networks for Delivering Active Substances to Selected Environments." The most effective enteric materials include polyacids having a pK_a of from about 3 to 5. Exemplary materials include fat-fatty acid mixtures ethyl cellulose, cellulose acetate phthalates, and the like.

Also suitable as enteric coatings are various poly(meth)acrylates which may be introduced to the polymeric carrier particles or dosage form either by *in situ* polymerization or by absorption of an aqueous dispersion of the materials. Suitable poly(meth)acrylates include copolymers of methylmethacrylate and ethylacrylate as ester components with methacrylic acid which contain carboxylic

groups that are transformed to carboxylate groups at a pH of from about 5 to 7. They are thus able to form water-insoluble materials which are resistant to gastric juices and methacrylate ester copolymers which are insoluble over the entire physiological pH range.

Specific copolymers useful as enteric materials are as follows.

Enteric Material	Molecular Weight	Preferred Monomer Ratio
poly (methacrylic acid, ethylacrylate) copolymer	250 kD	1:1
poly (methacrylic acid, methylmethacrylate) copolymer	135 kD	1:2 to 1:2
poly (ethylacrylate, methacrylate) trimethyl-ammoniaethylmethacrylate chloride	150 kD	1:2:0:2
poly (ethylacrylate, methylmethacrylate) trimethylammoniaethyl-methacrylate chloride	150 kD	1:2:0:2

The enteric coating may be applied on the polysaccharide-coated microparticles containing the active agent. While the delivery vehicle is a dosage form such as tablets, the enteric coating may be applied either on the microparticles which are compressed to form the tablets or directly on the tablets. For a capsule formulation, it is preferred that the enteric coating is applied on the microparticles containing the active agent and the enteric coated particles in admixture with pharmaceutically acceptable excipients are then filled into the gelatin capsules.

IV. Uses of the Present Invention

As noted above, the present invention is directed to the treatment of different types of diseases of the colon. In

the preferred embodiment the composition and method is particularly suited for the treatment of inflammatory bowel disease. Preferred drugs utilized in the dosage form for treatment of inflammatory bowel disease include hydrocortisone, beclomethasone dipropionate, tixocortol pivalate, budesonide, dexamethasone, prednisone, prednisolone and triamcinolone acetonide. In addition to the preferred corticosteroids, nonsteroidal anti-inflammatory agents are also contemplated, such as amino salicylate and sulfasalazine. In addition, other agents which have been found to beneficially treat anti-inflammatory bowel disease may be delivered by the present composition and method. For example, recent clinical studies have shown that ulcerative colitis may be beneficially treated with cyclosporine, a drug that has usually been given to transplant patients. Another class of drugs that is contemplated is referred to as prodrugs wherein they are entrapped in the polymeric particles in the same manner as the preferred drugs previously mentioned. Examples of prodrugs are dexamethasone-succinate-dextran (Gastroenterology, 1994, 106:2 405-413), budesonide-β-D-glucuronide (Gut, 1994, 35: 1439-1446), and dexamethasone-β-D-glucuronide (Pharm. Res., 1993, 10: 1553-1562).

With respect to the treatment of colonic malignancies, a suitable antitumor agent which is known in the art for the treatment of localized malignancies will be incorporated in the dosage form. Examples of antitumor agents suitable for use in this invention are methotrexate, 5-fluorouracil, and similarly functioning antineoplastic agents, such as tamoxifen, cyclophosphamide, mercaptopurine etoposide, indomethacin, semustine, fluorouracil, floxuridine and mitomycin. For the treatment of infections of the colon, antibiotics (including antibacterials) which are suitable for use in this invention include sulphanilamides and their derivatives, and other antibiotics specifically designed to treat particular bacterial infections associated with food

ingestion. Additional examples include sulfonamides, norfloxacin, chloramphenicol, tetracyclines and vancomycin.

For treatment of parasites, suitable antiparasitic agents include diloxanide furoate, metronidazole, quinacrine, tetracyclines, iodoquinol, dehydroemetine, amphotericin B, mebendazole and thiabendazole.

The following examples are submitted for illustrative purposes only and should not be interpreted as limiting the invention in any way. A person of ordinary skill, informed of this invention, will readily think of other delivery vehicles, or other active agents, or other intestinal diseases that can be readily substituted in the following examples. Also, the patents and publications cited in this disclosure reflect the level of skill the art to which this invention pertains, and are herein individually incorporated by reference to the extent that they supplement, explain, provide a background for or teach methodology, techniques and/or compositions employed herein.

Preparation 1

Nonporous Microspheres Containing Budesonide

This example was adapted from Lee et al., Science, 213:233-235 (1981).

Budesonide (10 mg) was suspended in 0.8 ml of sodium phosphate buffer (1 mM, pH 7.5) containing sodium dodecyl sulfate (1.0 percent). Bovine serum albumin (200 mg) was then dissolved in the suspension and kept at 4°C. Polymerization was initiated by the addition 0.2 ml of glutaraldehyde, making the final concentration 1 percent. The system was rapidly mixed, pipetted into 100 ml of an oil phase (corn oil and petroleum ether, 1:4 by volume), and stirred at room temperature. A water-in-oil emulsion formed. Although crosslinking of the protein in the emulsified droplets is

complete in 10 minutes, the reaction mixture was stirred continuously for one hour before the oil phase was decanted. The resulting beads were washed three times with petroleum ether and dried in a vacuum desiccator. The size of the beads depends on the speed of stirring. This procedure consistently produced beads of 100 to 200 μm.

Preparation 2

Microcapsules Containing Budesonide

This example was adapted from Lim, Biomedical Application of Microencapsulation, page 76. In the example, budesonide is encapsulated using a solvent evaporation procedure.

Five to 6 mL of 34 wt% poly(lactic acid) in chloroform is mixed with 10 mg budesonide with a stainless steel turbine stirrer at low speed (50 rpm) in a 100 mL beaker suspended in a water bath heated to 65°C. When all the budesonide has dissolved in the poly(lactic acid) solution, glycerine (50 mL) at 65°C is added, and the stirrer speed is increased to 800 rpm to form a dispersion of the organic solvent in glycerine. The stirring is continued for 5 to 6 min. to evaporate some of the solvent from the dispersed droplets. During this time, 600 mL of freshly prepared 0.1% sodium oleate solution is stirred in a 1.5 L beaker with a 3.5 cm Teflon®-coated magnetic stirrer at a speed high enough to form a vortex to the bottom of the beaker. The glycerine/chloroform/poly(lactic acid)/budesonide dispersion is added dropwise to the oleate solution to harden the microcapsules and to also remove the remaining solvent. A slow stream of air is blown over the surface of the soap solution to facilitate the removal of chloroform vapors. Other suspending agents such as gelatin, poly(vinyl alcohol) and Tergitol® can also be used.

After 10 min. of aeration, ice cubes (100 to 200 g) are added to the soap solution to bring the temperature below 10°C. The slurry is immediately filtered on a Buchner filter, washed with 400 mL soap solution, air dried overnight, washed with water to remove the soap, and air dried again before sieving.

Preparation 3

Microparticles Containing Budesonide

This example was adapted from Guiot and Couvreur, Polymeric Nanoparticles and Microspheres, page 13.

A solution (10 mL) of 1% gelatin and 0.5% Polysorbate 20 was made and equilibrated at 35°C. Seven mL of 20% w/v sodium sulfate and 10 mg budesonide were added while stirring with a magnetic stirrer bead until the solution acquired a faint permanent turbidity. Sufficient isopropanol was then added until the turbidity disappeared. A Silverson Laboratory Mixer Emulsifier, fitted with a 0.625-in. head was used to agitate the system as 0.6 mL of a 25% aqueous glutaraldehyde solution was added in 1 aliquot. The hardening process was allowed to continue for 20 minutes at 35°C when it was terminated by the addition of 5 ml of a 12% sodium metabisulfite solution. The crude mixture was shell frozen in a dry ice/acetone bath and lyophilized overnight on a FD_2 Dynavac Freeze Dryer. Upon reconstitution in 10 mL of 0.04% chlorbutol solution, the mixture was desalted on a Sephadex G-50 column. The void volume containing the microparticles is then freeze-dried to isolate the microparticles.

Preparation 4

Non-crosslinked Porous Beads

A two-liter four necked reaction flask equipped with a stirrer driven by a variable speed motor, reflux condenser,

thermometer, and nitrogen-inlet tube was set up. A slow flow of nitrogen was maintained through the reaction flask at all times. An aqueous phase made up at 350 parts of deionized water, 1.8 parts of gum arabic, and 1.8 parts sodium lignosulfate (Marasperse-N 22 available from Reed Lignin Inc.) was added to the flask and an organic solution made up 87.25 parts of styrene, 71.35 parts of heptane, and 2.2 parts benzoyl peroxide (70% active ingredient and 30% water) was dispersed in the aqueous phase with rapid agitation (stirrer speed approximately 950 rpm) to obtain a plurality of droplets having an average droplet diameter of below about 60 microns as determined by visual observation of a sample of the droplets with an optional microscope.

The reaction mixture was then heated to about 75°C and maintained at that temperature for 10 hours to form porous beads of non-crosslinked polystyrene having heptane entrapped within the pores. The reaction mixture was then cooled to room temperature and the resulting polymeric beads collected by filtration, washed three times with 1000 parts of deionized water, and three times with 1000 parts of acetone, then dried in a vacuum oven at 90°C for 24 hours.

Example 1

Liposomes Containing Budesonide

This example was adapted from van Rooijen, Advances in Biotechnological Processes, 13:255-279 (1990).

75 mg of phosphatidylcholine, 11 mg of cholesterol and 10.6 mg of phosphatidic acid was dissolved in 20 mL methanol/chloroform (1:1) in a 500 mL round bottom flask. The organic phase was then removed by low vacuum rotary evaporation at 37°C. The lipid film was dissolved in 10 mL of chloroform containing 10 mg budesonide, followed by

evaporation of the chloroform by low vacuum rotary evaporation at 37°C. The thin film that formed on the interior of the flask was dispersed in 10 mL phosphate-buffered saline (PBS) by gentle rotation for 15 minutes at room temperature. After complete removal of the lipid film from the interior of the flask, the white milky suspension was kept for 2 h. at room temperature. It was next sonicated for 3 min. at room temperature in a water bath sonicator and kept suspended for another 2 hours at room temperature. The suspension was next centrifuged at 100,000 g for 30 minutes at 16°C to isolate the liposomes. The liposomal dispersion can then be mixed with pectin, in the appropriate proportions, for further encapsulation in the gelatin capsules as described above. Because liposomes are fragile, they are not suitable for use in tableting procedures.

Example 2

Tablet Formulation

Tablets containing a suitable amount of the active agent entrapped in a delivery as described in Preparation 1, 2, 3 or 4 can be prepared with the following general formulation:

Tablet Component	Weight (mg)
Delivery system with corticosteroid	250
Pectin	200
Dibasic calcium phosphate	100
Eudragit™ 100S	100
Magnesium Stearate	10

Tablets are prepared by mixing the indicated amount of delivery vehicle containing the active agent as described above in Preparation 1, 2, 3 or 4 with ingredients listed in the formulation except Eudragit™. Tablets are produced by compression compaction using a stainless steel mold and a suitable hydraulic press. These tablets are then pan-coated with the Eudragit™ 100S to provide an enteric coating that

will allow the tablets to traverse through the stomach without disintegration or premature release of the drug. To coat the tablets, they are placed in a suitably heated rotating drum at about 40-45°C and, while rotating, an appropriate amount of an Eudragit™ solution in ethanol, isopropanol or acetone is slowly added to the tumbling tablets to obtain a uniform coating by evaporation of the solvent.

Example 3

Preparation of Delivery System Dispersed in Pectin

A pectin solution is prepared by dissolving 1.5 g of pectin (moistened with 0.5 ml of ethanol to facilitate dissolution) in 30 ml of water heated to about 50°C. The suspension is maintained at this temperature with gentle stirring until a clear, viscous solution is obtained. Then, 2.5 g of delivery system containing the corticosteroid and prepared as described in Preparation 1, 2, 3 or 4 above is placed in a suitable glass or metal container such that it can be rotated while heated and its contents stirred to prevent agglomeration. The pectin solution is then added slowly and in small portions to the delivery system, while rotating the vessel and continue heating. As the mixture dries, more pectin solution is added until completion. A granular material, with granules about 0.6-1.0 mm in diameter is obtained. Larger clumps are easily broken into smaller particles with a glass rod or other suitable utensil.

The dry material thus obtained is divided into 400 mg portions, and each is placed in a gelatin capsule. Alternatively, if smaller capsules are desired, 200 mg portions can be used. These capsules, properly sealed, are then placed in a mildly heated coating pan (about 40°C) and, while rotating, an Eudragit™ 100S solution in ethanol, isopropanol or acetone is slowly added to the tumbling capsules to obtain a uniform coating when the solvent evaporates.

WHAT IS CLAIMED IS:

1 A composition for treating diseases of the distal intestinal tract, comprising:

(a) a controlled release delivery vehicle selected from the group that consists of nonporous microspheres, microcapsules, non-crosslinked porous beads and liposomes which enclose a therapeutically effective amount of an active agent, and
(b) a polysaccharide that initially remains intact in the gastrointestinal tract and degrades in or near the large intestine, whereupon said active agent is released at a controlled rate.

2. The composition of Claim 1 wherein said composition further comprises an enteric blocking agent to protect said composition against degradation by acid conditions in the stomach.

3. The composition of Claim 1 wherein said nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes are surrounded with said polysaccharide that remains intact until it is degraded by distal intestinal tract bacteria to thereby release said active agent in the distal intestinal tract.

4. The composition of Claim 3 wherein said polysaccharide is pectin.

5. The composition of Claim 1 wherein said active agent is selected from the group consisting of corticosteroids and nonsteroidal anti-inflammatory agents for treatment of inflammatory bowel disease, antitumor agents for treatment of colonic malignancies, antiparasitic agents for treatment of

parasites, and antibiotics for treatment of infections.

6. The composition of Claim 1 wherein said active agent is present in said composition in an amount of about 1-100 mg.

7. The composition of Claim 1 wherein said composition is formulated for treating inflammatory bowel disease and said active agent is a corticosteroid selected from the group consisting of hydrocortisone, beclomethasone dipropionate, tixocortol pivalate, dexamethasone, prednisone, budesonide and prednisolone and triamcinolone acetonide.

8. The composition of Claim 1 wherein said composition is a tablet prepared from compression of a mixture comprising said nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes and said polysaccharide is compressed into said tablet or coated thereon.

9. The composition of Claim 1 wherein said composition is a capsule comprising said nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes and said polysaccharide is coated on said nonporous microspheres, microcapsules, non-crosslinked porous beads or liposomes or on said capsule.

10. The composition of Claim 8 further comprising an enteric blocking agent coated on said tablet as an exterior layer.

11. The composition of Claim 9 further comprising an enteric blocking agent coated on said nonporous

microspheres, microcapsules, non-crosslinked porous beads or liposomes.